REMARKS

Reconsideration and reexamination of the subject application are respectfully requested in light of the foregoing amendments and following remarks.

1. Status of the claims

Claims 1-12 and 18-25 are pending in the application. All claims stand rejected.

2. Support for the amendments

Support for an agnoprotein "comprising" the amino acid sequence of SEQ ID NO: 1 can be found in the specification at page 14, lines 23-29 and page 16, line 14, *et seq.* (fusion proteins), for example.

3. Rejection under 35 U.S.C. § 112, second paragraph

Claims 12 and 18-25 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Office Action, page 5. Specifically, the Examiner apparently questions whether the cells "derived" from a glioblastoma are obtained from a glioblastoma cell line. The term "derivatives" is not at issue in the rejection.
The claim term at issue appears in subsection (iii) of claim 12 (emphasis added):

> (iii) one or more derivatives of agnoprotein, wherein the amino acid sequence of said one or more derivatives have at least about 83% sequence identity to SEQ ID NO: 1, and wherein said one or more derivatives have cell growth inhibitory activity,
> such that growth of cells ***deriving*** from the glioblastoma is inhibited.

Giving the term its plain meaning, "deriving" is used in context as an intransitive verb, meaning "to issue from a source; originate." *See, e.g.*, THE AMERICAN HERITAGE COLLEGE DICTIONARY, 4th ed., Houghton Mifflin Co., New York (2004). That is, the recited cells issue from or originate from the glioblastoma. This meaning is consistent with the specification's teaching at page 18, lines 29-32, for example, where the agnoprotein is administered to cells from malignant cancers having their origin in various tissues or organs. Particularly, there is no explicit or implied step in which the artisan

first "obtains" a cell before administering an agnoprotein. The term is definite from its plain meaning, and the rejection accordingly should be withdrawn.

4. Rejections of the claims under 35 U.S.C. § 112, first paragraph (written description requirement)

[A]

Claims 1-5, 8, 12-19, and 22[1] are rejected under 35 U.S.C. § 112, first paragraph, as allegedly inadequately described in the specification. Office Action, page 3. Applicant traverses the rejection. The rejection is based solely on the claim language "one or more agnoproteins," appearing in claims 1 and 12. This language does not appear in the amended claims, mooting the rejection.

[B]

Claims 1-12 and 18-25 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing impermissible new matter. Specifically, the Examiner alleges that "one or more biologically active fragments of agnoprotein, wherein said one or more fragments comprise amino acid residues 1-36 of SEQ ID NO: 1" is not supported in the specification as filed. The Examiner acknowledges support for the claim element at page 37, lines 5-11 (e.g., "GST-Agno 1-36"), but alleges that this description does not support the recited activity of inhibiting cell growth. Applicant traverses the rejection.

"New matter" rejections are properly reviewed under § 112, first paragraph. *See In re Rasmussen*, 650 F.2d 1212, 1214, 211 U.S.P.Q. 323, 325 (C.C.P.A. 1981). Reduction to practice is not required to comply with the written description requirement. *See Falkner v. Inglis*, 79 U.S.P.Q.2d 1001, 1007-08 (Fed. Cir. 2006). Nor do Applicants need to disclose or even understand why an invention works. *See, e.g., Newman v. Quigg*, 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989). The Examiner bears the burden of providing reasons or evidence why the written description requirement is not met. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

In the present case, GST-Agno 1-36 is a representative example of a biologically active fragment of an agnoprotein, where the fragment comprises amino acid residues

[1] The rejection also applies to canceled claim 26, presumably through typographical error. Clarification is requested.

1-36 of SEQ ID NO: 1, as recited. The specification discloses that GST-Agno 1-36 associates with p53. *See, e.g.*, Specification, page 37, lines 5-15. The specification further discloses that the interaction between this region of agnoprotein and p53 may contribute indirectly to the inhibition of cell growth effected by agnoprotein. *See, e.g.*, Specification, page 37, lines 16-20. The specification thus provides objective evidence that reasonably would lead the skilled artisan to conclude that GST-Agno 1-36, like full length agnoprotein, inhibits cell growth. The specification does not need to provide more to comply with the written description requirement. In particular, the specification does not need to show reduction to practice of GST-Agno 1-36 in a method of inhibiting cell growth, nor does the specification need to disclose why agnoprotein works. *See Falkner*, 79 U.S.P.Q.2d at 1007-08; *Newman*, 11 U.S.P.Q.2d at 1345. The Examiner provides no reason or evidence to doubt the disclosure of a connection between p53 binding and the activity of agnoprotein in inhibiting cell growth. *See Alton*, 76 F.3d at 1175. The specification need only "convey with ***reasonable clarity*** to those skilled in the art that, as of the filing date sought, [applicant] was in possession of the invention." *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991) (emphasis added). For the reasons set forth above, the specification shows possession with the requisite level of clarity, and the rejection accordingly should be withdrawn.

5. Rejection of the claims under 35 U.S.C. § 112, first paragraph (enablement requirement)

All the claims are rejected under 35 U.S.C. § 112, first paragraph, as alleged requiring undue experimentation to practice the claimed methods. Applicant traverses the rejection.

Applicant's reasons for traverse set forth in the Response filed Feb. 7, 2008

For clarity of the record, Applicant repeats the traverse in the Response filed Feb. 2, 2008. The skilled artisan was aware of over 100 agnoprotein sequences that are useful for practicing the presently claimed invention, evidencing that the state of the relevant art was highly advanced. Also as set forth above, the specification provides experimental evidence of agnoprotein fragments that possess the relevant biological activity. As further set forth above, the specification, combined with the advanced state of the art,

provides an agnoprotein consensus sequence. For the reason stated above, the consensus sequence allows the artisan to make and/or use predictably the claimed agnoprotein derivatives. Accordingly, the enabling teachings of the specification are commensurate with the scope of the presently claimed invention. *See In re Fisher*, 166 U.S.P.Q. 19, 24 (C.C.P.A. 1970).

With respect to the experimentation required to practice the invention, the specification further provides a number of routine cell culture assays useful to screen agnoproteins for biological activity. *See* Specification, page 30, line 1 *et seq.* (expression of agnoprotein in glial cells to assay an effect on cell cycle progression); page 32, line 7, *et seq.* (suppression of cell proliferation in NIH 3T3 cells); page 33, line 19, *et seq.* (using NIH 3T3 cells to determine the effect of agnoproteins on cyclins A and B, p27, p21, and p53, which modulate the cell cycle).

The specification provides a ***working example*** of the efficacy of agnoproteins in a method of inhibiting cell growth. Specifically, the specification demonstrates efficacy of agnoprotein in the U87MG glioblastoma cell line. *See, e.g.*, Specification, Example 1. Efficacy in a cell model or animal model constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. *See* Manual of Patent Examining Procedure (MPEP), § 2164.02, "Working Example," 8th ed., revised Aug. 2006, under the subheading "Correlation: *In Vitro/In Vivo*." Whether a correlation between an *in vitro* model and a method of treating a disease exists must be determined ***from the perspective of one skilled in the art***—not from the perspective of the Office:

> If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). MPEP § 2164.02.

In this regard, only a reasonable correlation is required—not a rigorous or an invariable exact correlation. MPEP § 2164.02 (citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)).

When viewed from the standpoint of the correct legal standard, the skilled artisan would accept successful tests for efficacy in the human U87MG glioblastoma cell line as correlating with a method of treating glioblastoma *in vivo*. Applicant previously submitted appropriate evidence that chemotherapy drugs tested for efficacy *in vitro* using U87MG glioblastoma cells were considered candidates for further testing *iv vivo*. *See* Zhao *et al.*, *Int'l J. Oncol.* 21: 49-55 (2002) ("Zhao"; submitted in an IDS filed herewith); Yoshida *et al.*, *Neurosurgery* 39: 360-66 (1996) ("Yoshida"; submitted in an IDS filed herewith). The skilled artisan used U87MG cells expressly because the efficacy of a compound in this cell line indicated the potential usefulness of the compound for *in vivo* treatment. *See, e.g.*, Ex. 3, p. 49 ("The present evidence that As_2O_3 at relatively low concentration effectively inhibited proliferation of U87MG and T98G cells *in vitro*, suggests that the drug may be considered for *in vivo* testing on animal models and possibly clinical trials on glioma patients."); Ex. 4, *2 ("This [*in vitro*] study was designed to determine whether the motility and invasiveness of glioblastoma cells could be influenced by treatment with [estramustine phosphate] and to correlate those findings with the ability of the agent to inhibit proliferation. Suppression of the infiltrative capacity of malignant glioma cells could be of significant value in the treatment of those lesions."). Nothing more can logically be required to find that the skilled artisan would find that the *in vitro* model "correlates" with an *in vivo* application.

In the previous Office Action, the Examiner alleged throughout that successful clinical tests are required to comply with the enablement standard. *See* Office Action, pages 9-10. The Office produced ***no authority*** that 35 U.S.C. § 112, first paragraph, sets forth a statutory requirement for applicants to provide successful results in a clinical trial for approval of a patent. To the contrary, it has been well established for over a decade that successful clinical trials are not a *sine quo non* for invention. *See In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (reversing a rejection under 35 U.S.C. § 112, first paragraph, and holding that the demand for successful clinical trials is unduly burdensome and not required to prove even utility).

For all these reasons, the presently claimed invention comports with the legal requirements for an enabling disclosure under 35 U.S.C. § 112, first paragraph, and the rejection may be withdrawn.

The Office's response to Applicant's traverse

In the Office Action mailed March 19, 2008, the Examiner acknowledges that Applicant considers the U87MG glioblastoma cell line is a model recognized as correlating to a specific condition, i.e., glioblastoma. The Examiner, however, alleges that Zhao and Yoshida were not attached with Applicant's response. Applicants submits Zhao and Yoshida in an IDS filed herewith and requests consideration of both references. In any event, the Examiner discounts both references on the following grounds:

> [T]hese references indicate that the *in vitro* data indicates a ***potential*** usefulness in *in vivo* treatment and that the drug ***may be considered*** to [sic] *in vivo* testing on animals. Thus, those skilled in the art clearly recognize that while *in vitro* data is a precursor to *in vivo* testing, it does not mean that the drug will be effective *in vivo* (absent *in vivo* data).

Office Action, page 4 (emphasis in original).

The MPEP states: "'Correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." MPEP § 2164.02. The MPEP clearly requires the Office to consider correlation between an *in vitro* assay and a claimed method of use. For this reason, *in vitro* data cannot be discounted merely because the data indicate a potential usefulness *in vivo*. After all, skilled artisan uses *in vitro* assays precisely because of the expected potential usefulness of the results in predicting *in vivo* efficacy. The MPEP specifically condones such a use of *in vitro* testing. *See Id.*

The MPEP requires the Examiner to "weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *Id.* The only evidence the Office advances is the conclusory remark that drugs that work *in vitro* will not necessarily work *in vivo*, because the art is unpredictable. The MPEP, however, clearly states that Applicant can comply with the enablement requirement in the absence of *in vivo* testing. It is always the case that *in vitro* testing, as well as *in vivo* testing for that matter, may not rigorously

correlate with efficacy in treating a disease in a patient. Clinical trials are required to determine this level of efficacy. But neither clinical trials nor a rigorous correlation are required to show enablement. *See* MPEP § 2164.02 (relying on *Brana* and *Cross*). For the reasons above, Applicant complies with the relevant requirements for enablement. The rejection thus is improper and should be withdrawn.

The Examiner attempts to distinguish the holding in *Brana*, because *Brana* related to compositions, not methods. Office Action, page 5. The Examiner provides no evidence, such as text from the *Brana* decision, to suggest that the holding was so limited. The MPEP acknowledges in its discussion of *Brana*, set forth above, that the *Brana* decision was not so limited. The Examiner is bound by the MPEP, as well as Federal Circuit precedent. *See* MPEP, Forward. The Examiner further attempts to distinguish *Brana* on the grounds that the cell lines at issue in *Brana* were recognized by the NCI as providing evidence of efficacy that correlated with *in vivo* use. Zhao and Yoshida provide the same evidence in the present case. The Office has not distinguished the holding in *Brana*. Applicant complies with the proper standard for providing an enabling disclosure, as set forth in the MPEP and cases cited therein, for example. The rejection thus is improper and should be withdrawn.

CONCLUSION

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is respectfully requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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